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SYNTHESIS OF CERTAIN SUBSTITUTED 7-CHLORO-4-QUINAZOLONES OF PHARMACEUTICAL INTEREST

Mohamed I. Al-Ashmawi*, Mohamed A. Shabaan and Refaat H. Omar

Department of Organic Chemistry, Faculty of Pharmacy,

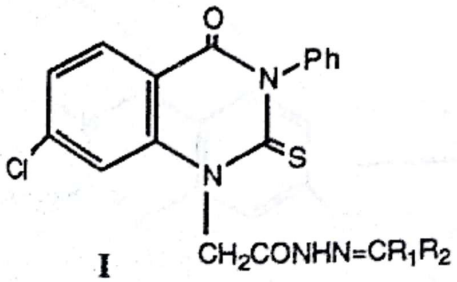
** University of Zagazig and Cairo Univerdsity*

ABSTRACT

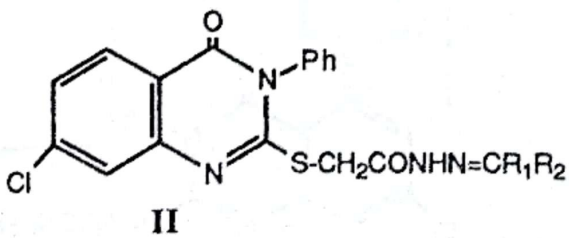
The synthesis of some N-(7-chloro-3-phenyl-4 (3H)-quinazolinon-2-ylmercaptoacetyl) hydrazones is described. Reacting 7-chloro-3-phenyl-4-quinazolinone-2-thione with ethyl chloroacetate yielded two isomeric esters. Condensation of these esters with hydrazine hydrate under different reaction conditions afforded the expected hydrazides in addition to some sulphur free products.

INTRODUCTION

6-Bromo and 7-chloro 1,2,3,4-tetrahydroqinazoline 2,4-diones[1,2], as well as certain 7-chloro-2,3-disubstituted 3,4-dihydroquinazolin-4-ones[3,4] have been reported to be useful as non-steroidal analgesic and anti-inflammatory agents.



I



II

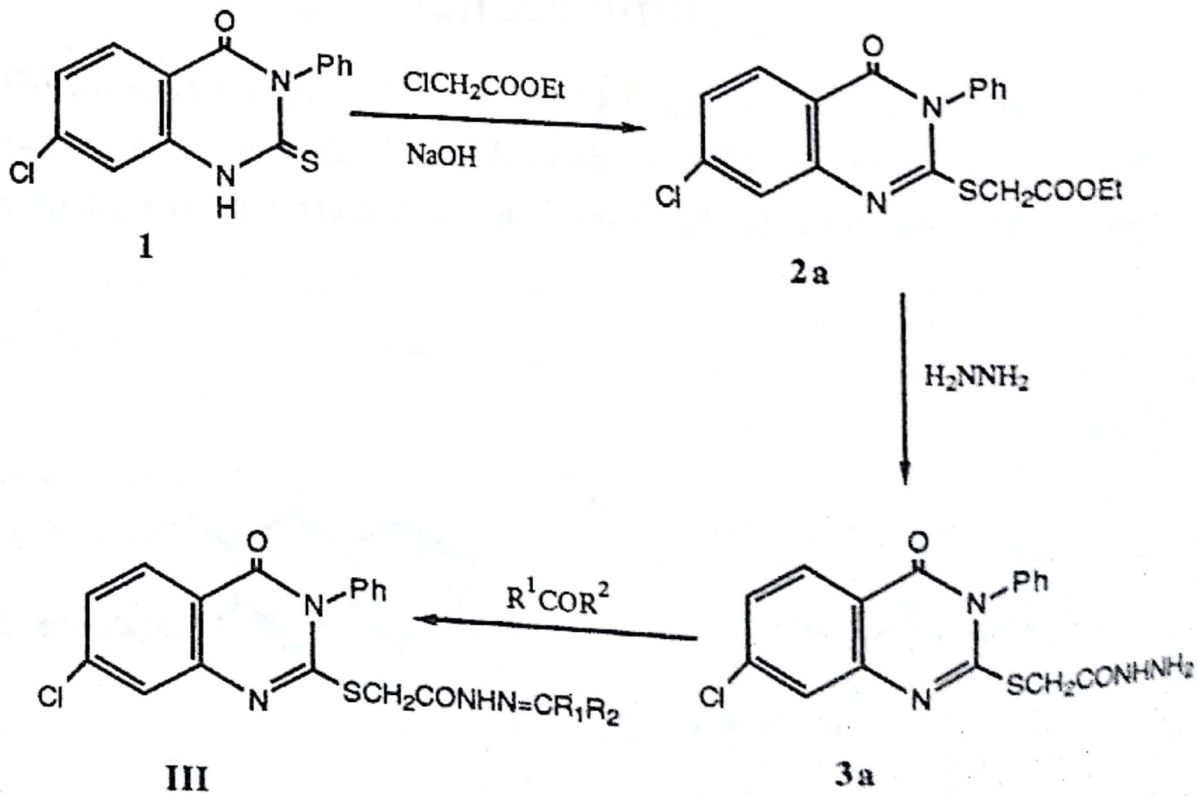
R^1, R^2 = H, alkyl or aryl residues

Accordingly, the authors decided to synthesize compounds of the general formulae I and II in search for anti-inflammatory agents with better therapeutic effects.

RESULTS AND DISCUSSION

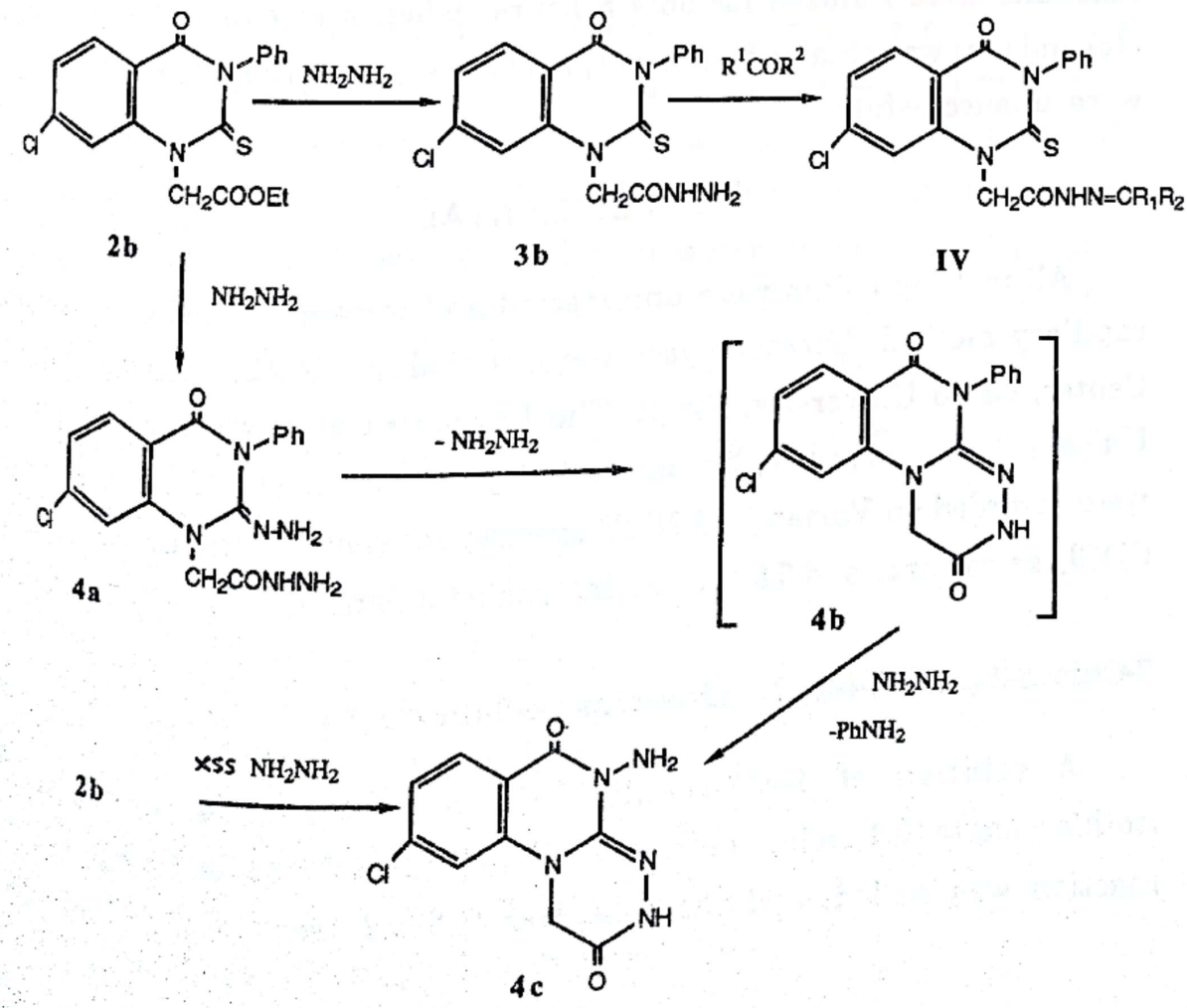
4-Chloroanthranilic acid was prepared from 4-chloro-2-aminotoluene according to reported procedures[5,6]. Condensation of this acid with phenyl isothiocyanate afforded 7-chloro-3-phenyl-4-quinazolinone-2-thione, which was used for the preparation of the target compounds, (Schemes 1 and 2):

Scheme 1:



Reacting 7-chloro-3-phenyl-1,2,3,4-tetrahydro-4-quinazolinone-2 thione with ethyl chloroacetate in ethanolic sodium hydroxide on cold afforded two products of different melting points and different IR spectra, but having identical microanalytical data. From the IR data and a careful consideration of the possible reaction pathways, it was evident that the products in hand were the ethylester of S-and N acetates respectively. The percentage yield of the above esters was decreased on carrying the reaction at the reflux temperature or by using stronger bases such as sodium ethoxide, which may be ascribed to the facile elimination of the sulphur atom of compound (1). This was confirmed by the isolation of 7-chloro-3-phenyl-2,4-quinazolinedione as a by-products[7].

Scheme 2:



The reaction of 7-chloro-3-phenyl-1,2,3,4-tetrahydro-1(-ethoxycarbonyl-methyl)-4-quinazolinone-2-thione (1b) and excess hydrazine hydrate was also studied. Conducting the reaction under reflux for 12 hours gave an acidic product, free from sulphur, and its microanalytical data suit to structure (4c).

The NMR data revealed the absence of phenyl protons at position 3 confirming the same structure. Furthermore, consulting the literature[8], it was found that 3-aryl-4-quinazolinones underwent the same rearrangement into 3-amino-4-quinazolinones by the effect of excess hydrazine hydrate at high temperatures, (Scheme 2).

In an attempt to isolate the reaction intermediates (4a) and (2b), the reactants were refluxed for only 5 hours when a mixture of compounds (4c) and (4a) was obtained. However, trials to separate the intermediate (4b) were unsuccessful.

EXPERIMENTAL

All melting points were uncorrected and were measured by the open capillary method. Microanalyses were carried out in the Microanalytical Center, Cairo University, Egypt. The IR spectra were recorded on a Pye Unicam SP 1100 spectrophotometer using KBr discs. The ^{1}HNMR spectra were recorded on Varian T60 NMR spectrophotometer using DMSO-d_6 and $CDCl_3$ as solvents and TMS as an internal standard.

7-Chloro-3-phenyl-4-(3 H) quinazolinone-2-thione (1):

A solution of 4-chloroanthranilic acid (0.1 mole) and phenyl isothiocyanate (0.1 mole) in ethanol (150 ml) was refluxed for 1.5 hours. The reaction was cooled, and the solid was filtered, washed with cold 10%

aqueous sodium carbonate solution then water. Recrystallization from ethanol afforded the pure product, m.p. above 300°C yields 78%.

IR: 1690 cm^{-1} (C=O at position 4), 1350 cm^{-1} (C=S), 3170 cm^{-1} (NH).

$C_{14}H_9N_2OCIS$:

	C%	H%	N%
Calcd:	58.33	3.13	9.72
Found:	58.50	3.20	9.70

7-Chloro-3-phenyl-2-ethoxycarbonylmethylthio-4(3H)-quinazolinone (2 a) and 7-chloro-3-pheny-1-ethoxy-carbonylmethyl-4(3H)-quinazolinonel-2 thione (2 b):

Ethyl chloroacetate (0.01 mole) was dropped while stirring in a solution of (1) in absolute ethanol (20 ml) containing sodium hydroxide (0.01 mole). After one hour, the obtained heavy precipitate was filtered, washed with water, and recrystallized from ethanol giving 70% of (2a) m.p. 129°C. The filtrate was diluted with water, when a solid product separated, which on recrystallization from aqueous ethanol afforded 20% of the pure product which corresponds to (2b), m.p. 223°C.

IR for compound (2a): 1685 cm^{-1} (C=O at position 4), 1735 cm^{-1} (C=O of the ester).

IR for compound (2b): 1690 cm^{-1} (C=O at position 4), 1740 cm^{-1} (C=O of the ester).

$C_{18}H_{15}N_2O_3ClS$ (2b):

	C%	H%	N%
Calcd:	57.68	4.00	7.48
2 a : Found :	57.50	4.80	7.50
2 b : Found :	57.10	5.00	7.20

N-[(7-Chloro-3-phenyl-4(3H)-quinazolinon-2-yl)mercaptoacetyl] hydrazine (3a) and N-[(7-chloro-3-phenyl-4 (3H)-quinazolinone-2-thione-1-yl) acetyl] hydrazine (3b):

A mixture of 2 a or 2b (0.01 mole) and 95% hydrazine hydrate (0.02 mole) in absolute ethanol (20 ml) was heated under reflux for four hours. The white precipitate which resulted was filtered, washed with water and crystallized from ethanol to give the corresponding hydrazides 3a and 3b, m.p 195°C and above 300°C, respectively.

IR for compound (3 a): 1690 cm^{-1} (C=O at position 4),1670 cm^{-1} (C=O of the acetylhydrazine), 1650 cm^{-1} (C=N), 3170 cm^{-1} (NH).

IR for compound (3b): 1690 cm^{-1} (C=O at position 4), 1670 cm^{-1} (C=O of the acylhydrazine), 3180 cm^{-1} (NH).

$C_{16}H_{13}N_4O_2ClS$:

	C%	H%	N%
Calcd:	58.45	3.96	17.05
2 a : Found:	58.30	3.80	17.00
2 b : Found :	57.90	3.70	17.30

7-Chloro-4-oxo-3-phenyl-1-hydrazinoacetyl-1,2,3,4-tetrahydroquinazoline-2-hydrazone (4 a) and 10-amino-6-chloro-4H-2,3,9,10-tetrahydro-1,2,4a,10-tetrazaphenathrene-3,9-dione (4 c):

A mixture of (2b) (0.01 mole) and hydrazine hydrate (15 ml) was refluxed for 5 hours. The reaction mixture was then cooled and the solid obtained was filtered, washed with water and recrystallized from ethanol to give compound (4a), m.p. 268°. Diluting the filtrate with water afforded compound (4 c). crystallization from ethanol gave the pure product m.p. 283°.

IR for compound (4a): 1690 cm^{-1} (C=O at position 4), 1675 cm^{-1} (C=O of the acylhydrazine), 1650 cm^{-1} (C=N), 3200 cm^{-1} broad (NH).

$C_{16}H_{15}N_6O_2Cl$:

	C%	H%	N%
Calcd:	53.58	4.18	23.43
Found :	53.80	4.00	23.70

IR for compound (4c): 1695 cm^{-1} (C=O at position 9), 1675 cm^{-1} (C=O of the triazine ring), 1650 cm^{-1} (C=N), 3180 cm^{-1} broad (NH).

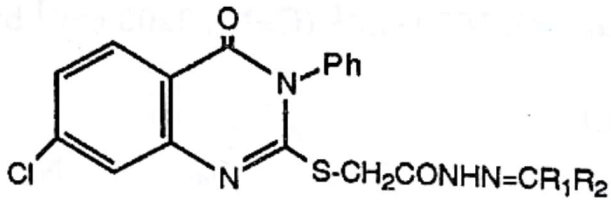
$C_{10}H_8N_5O_2Cl$:

	C%	H%	N%
Calcd:	45.18	3.01	26.30
Found :	45.20	3.10	26.00

N-[(7-Chloro-3-phenyl-4-(3H)-quinazolinon-2-yl-mercapto)acetyl] hydrazones III and N-[(7-chloro-3-phenyl-2-thione-4-(3H)-quinazolinon-1-yl) acetyl] hydrazones IV:

A mixture of (3 a) or (3b) (0.01 mole) and the appropriate carbonyl compound (0.01 mole) in absolute ethanol (25 ml) was allowed to react at room temperature for two hours. The separated product was then filtered, washed and recrystallized from ethanol (Tables I and II).

Table (I): N-[(7-Chloro-3-phenyl-4 (3 H)-quinazolinon-2-yl-mercaptoacetyl] hydrazones III.



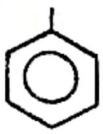
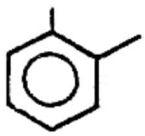
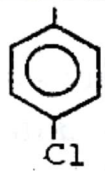
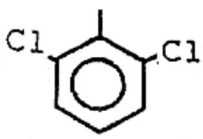
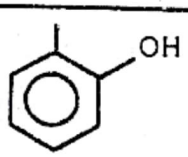
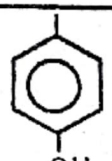
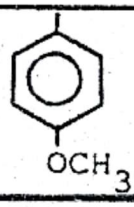
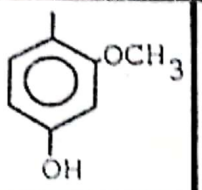
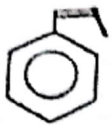
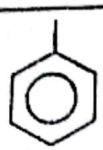
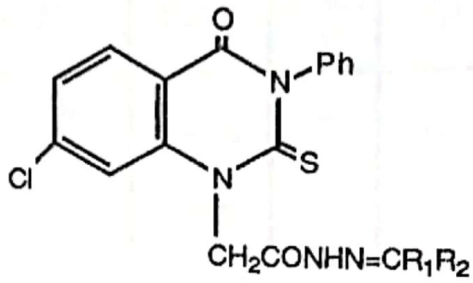
No.	R^1	R^2	Yield %	m.p.°C	Formula	Analysis %	
						Calcd	Found
1		H	80	259-9	$C_{23}H_{17}N_4O_2ClS$	C 61.53 H 3.79 N 12.47	61.20 3.50 12.30
2		H	82	244-5	$C_{23}H_{16}N_4O_2Cl_2S$	C 57.10 H 3.30 N 11.60	56.70 3.60 11.50
3		H	80	240-1	$C_{23}H_{16}N_4O_2Cl_2S$	C 57.14 H 3.31 N 11.59	57.00 3.30 12.10
4		H	85	212-3	$C_{23}H_{15}N_4O_2Cl_3S$	C 53.33 H 2.89 N 10.82	53.90 2.60 11.20
5		H	78	243-4	$C_{23}H_{17}N_4O_3ClS$	C 59.42 H 3.66 N 12.06	59.20 3.80 12.10
6		H	75	250-1	$C_{23}H_{17}N_4O_3ClS$	C 59.42 H 3.66 N 12.06	59.40 4.0 11.60
7		H	75	246-7	$C_{23}H_{19}N_4O_3ClS$	C 60.19 H 3.79 N 11.70	60.0 3.90 11.40

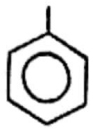
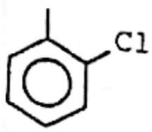
Table (I): (Cont.).

No.	R^1	R^2	Yield %	m.p.°C	Formula	Analysis %	
						Calcd	Found
8		H	65	209-10	$C_{24}H_{19}N_4O_4ClS$	C 58.24 H 3.84 N 11.32	56.70 3.50 11.00
9		H	70	217-9	$C_{25}H_{18}N_4O_2ClS$	C 63.22 H 4.00 N 11.80	62.90 4.00 12.30
10		H	70	226-7	$C_{25}H_{22}N_5O_2ClS$	C 61.04 H 4.48 N 14.24	61.00 4.50 14.10
11		CH_3	76	237-8	$C_{24}H_{19}N_4O_2ClS$	C 62.27 H 4.11 N 12.11	62.00 4.50 12.00
12		CH_3	85	231-2	$C_{19}H_{17}N_4O_2ClS$	C 56.93 H 4.25 N 13.98	57.20 4.40 13.50
13		C_2H_3	80	257-8	$C_{20}H_{19}N_4O_2ClS$	C 57.90 H 4.58 N 13.51	58.10 4.50 13.20
14		—	82	202-3	$C_{21}H_{19}N_4O_4ClS$	C 59.09 H 4.45 N 13.13	59.00 4.60 13.20
15		—	79	204-5	$C_{22}H_{21}N_4O_2ClS$	C 59.93 H 4.77 N 12.71	59.90 4.80 13.00

* Compounds listed showed the following general characteristics: 3200-400 cm^{-1} (NH and/or OH hydrogen bonded), 3060 cm^{-1} (CH aromatic), 1695 cm^{-1} (C=O at position 4), 1675-90 cm^{-1} (C=O of the acyl hydrazone), 1600-20 cm^{-1} (C=C, C=N).

Table (II): N-[(7-Chloro-3-phenyl-2-thione-4 (3H)-quinazolinon-yl) acetyl] Hydrazones IV.



No.	R^1	R^2	Yield %	m.p.°C	Formula	Analysis %	
						Calcd	Found
1		H	82	278-9	$C_{23}H_{17}N_4O_2ClS$	C 61.53 H 3.79 N 12.47	61.30 3.80 12.20
2		H	78	221-2	$C_{23}H_{16}N_4O_2Cl_2S$	C 57.14 H 3.31 N 11.59	57.40 3.20 12.00

* Compounds listed showed the following general characteristics: 3200 cm^{-1} (NH), 1695 cm^{-1} (C=O at position 4), 1675 cm^{-1} (C=O of the acyl hydrazone), 1345 cm^{-1} (C=S), 1600 cm^{-1} (C=N).

REFERENCES

(1) **Khalifa, M.; Osman, A.N.; Ibrahim, M.G.; Osman, A.E. and Ismail, M.A.;** Pharmazie, 37, 2 (1982).

(2) **Yabuuchi, T.; Fujimura, H.; Nakagava, A. and Kikura, R.;** Japan Kokai 7, 340,788 (Cl. 16E464), June 15, 1973. Appl. 7,178, 426, Oct. 07, 1971; C.A. 79, 66400 (1973).

(3) **Gallardo, A.S.A.;** Span, 360, 677, 16 July 1970, Appl. 25 Nov. 1968, C.A., 74, 100094 (1971).

(4) **Maillard, J.; Benard, M.; Vincent, M.; Von. Van-Tri; Jolly, R.; Morin, R. Benharkate, Mrs. and Menillet, C.;** Chim. Ther., 2, 231 (1967), C.A., 69, 36066 (1968).

(5) **Lutz, R.E.; Ashurn, G. and Wilson, J.W.;** J. Am. Chem. Soc., 68, 1285-8 (1946).

(6) **Magidson and Travins;** Gen. Chem. (U.S.S.R.), 7, 842 (1937).

(7) **Al-Ashmawi, M.I.; Badran, M.M. and Khalifa, M.;** Die Pharmazie, 31 (9), (1976).

(8) **Leonard, N.J. et al.;** J. Org. Chem., 11, 341 (1946).

تخليق بعض مركبات ٧-كلور-٤-كينازولون ذات الاهمية الصيدلية

محمد إبراهيم العشماوى* - محمد شعبان و رفعت حسين عمر

*قسم الكيمياء العضوية - كلية الصيدلة - * جامعة الزقازيق وجامعة القاهرة*

للمركب ٧-كلور-١ر٢ر٣ر٤-رباعى هيدروكينازولين -٢ر٤ - ديون تأثيرا مسكنا ومضاد للالتهابات . وفى هذا البحث حضرت مركبات مشابهه للمركب المذكور وتختلف عنه فى احتوائها على ذرة كبريت فى الموضع ٢- من حلقة الكينازولين .

بتفاعل ٧-كلورو-٣-فينيل- ١ر٢ر٣ر٤-رباعى هيدرو-٤-كينازرلينون -٢-ثيون مع كلورو اسيتات الايثيل نتج مزيج منن مشتقات ن - اسيتات وكب - اسيتات لهذها المركب وتم فصلهما وفوعل كل منها على حده مع هيدرات الهيدرازين ثم مع بعض الالديهيدات لتعطى النواتج النهائية المطلوبه .

كان تفاعل المركب الثانى مع الهيدرازين معتمدا على ظروف التفاعل فباستخدام مكافىء واحد من الهيدرازين تكونت المركبات المطلوبه . ولكن عند استعمال كمية كبيره من الهيدرازين تكونت مركبات ثلاثيه الحلقة خاليه من عنصر الكبريت . وقد تم التوصل الى التركيب البنائى لهذه المركبات .